

# Exhibit B

## Supplementary Online Content

O'Brien KM, Tworoger SS, Harris HR, et al. Association of powder use in the genital area with risk of ovarian cancer. *JAMA*. doi:10.1001/jama.2019.20079

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This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1.** Characteristics at Baseline by Cohort

	Nurses' Health Study I n=81,869	Nurses' Health Study II	Sister Study n=40,647	Women's Health Initiative
<b>Race</b>				
White	79,895 (98)	59,101 (96)	35,483 (87)	61,292 (84)
Black	1,196 (1)	826 (1)	3,293 (8)	5,735 (8)
Other	778 (1)	1,334 (2)	1,853 (5)	6,033 (8)
Missing	0	0	18	207
<b>Birth cohort<sup>a</sup></b>				
1915-1929	28,308 (35)	0 (0)	2 (0)	27,178 (37)
1930-1944	49,961 (61)	6 (0)	10,701 (26)	42,886 (59)
1945-1959	3,600 (4)	52,907 (86)	22,681 (56)	3,203 (4)
1960-1971	0 (0)	8,348 (14)	7,2623 (18)	0 (0)
<b>Education</b>				
High school or less	0 (0)	0 (0)	5,898 (15)	15,310 (21)
Some college	0 (0)	0 (0)	13,245 (33)	26,192 (36)
Completed college	81,869 (100)	61,261 (100)	21,498 (53)	31,179 (43)
Missing	0	0	6	586
<b>Body mass index (BMI; kg/m<sup>2</sup>)</b>				
<25.0 (Normal)	52,290 (64)	25,970 (43)	16,726 (41)	30,421 (42)
25.0-29.9 (Overweight)	19,793 (24)	18,017 (30)	12,591 (31)	24,768 (34)
>30 (Obese)	9,653 (12)	16,665 (27)	11,319 (28)	17,905 (25)
Missing	133	609	11	173
<b>Parity</b>				
Nulliparous	4,414 (5)	10,462 (17)	7,523 (19)	9,092 (12)
1 birth	5,726 (7)	8,375 (14)	5,856 (14)	6,396 (9)
2 births	22,828 (28)	24,345 (40)	15,022 (37)	18,997 (26)
3 or more births	47,479 (59)	18,079 (30)	12,221 (30)	38,352 (53)
Missing	1,422	0	25	430
<b>Smoking status</b>				
Never smoker	35,825 (44)	39,999 (65)	23,034 (57)	36,791 (51)
Former smoker	23,749 (29)	18,319 (30)	14,333 (35)	30,994 (43)
Current smoker	22,151 (27)	2,872 (5)	3,271 (8)	4,593 (6)
Missing	144	71	9	889
<b>Ever oral contraceptive use</b>	40,816 (50)	52,484 (86)	34,310 (84)	29,890 (41)
Missing	11	0	32	1
<b>Had tubal ligation</b>	14,402 (18)	16,603 (27)	11,698 (29)	12,609 (17)
Missing	22	0	16	388
<b>Had hysterectomy</b>	14,171 (17)	8,463 (14)	6,868 (17)	20,063 (27)
Missing	3	0	23	70
<b>Patent<sup>b</sup></b>	54,087 (66)	39,012 (64)	24,310 (60)	43,037 (59)
Missing	21	0	35	289
<b>Postmenopausal</b>	34,228 (42)	54,795 (89)	23,987 (59)	73,267 (100)
<b>Ever hormone therapy use</b>	13,919 (17)	27,590 (45)	15,098 (37)	39,777 (54)
Missing	18	113	121	1

<sup>a</sup>Approximation based on age at enrollment and median enrollment year; studies did not provide exact dates<sup>b</sup>No hysterectomy or tubal ligation

**eTable 2.** Characteristics at Baseline by Use of Powder in the Genital Area

	<b>Never User of Powder</b> n= 158,084	<b>Ever User of Powder</b> n= 98,960
<b>Study</b>		
Nurses' Health Study	48,429 (31)	33,440 (34)
Nurses' Health Study II	45,096 (29)	16,165 (16)
Sister Study	29,807 (19)	10,840 (11)
Women's Health Initiative	34,752 (22)	38,515 (39)
<b>Race</b>		
White	145,996 (92)	89,775 (91)
Black	5,151 (3)	5,899 (6)
Other	6,825 (4)	3,173 (3)
<b>Education</b>		
High school or less	12,234 (8)	8,974 (9)
Some college	21,672 (14)	17,765 (18)
Completed college	123,880 (79)	71,927 (73)
<b>Body Mass Index (BMI; kg/m<sup>2</sup>)</b>		
<25.0 (Normal)	82,681 (53)	42,726 (43)
25.0-29.9 (Overweight)	45,186 (29)	29,983 (30)
≥30 (Obese)	29,630 (19)	25,912 (26)
<b>Parity</b>		
Nulliparous	20,153 (13)	11,338 (12)
1 birth	16,690 (11)	9,663 (10)
2 births	51,328 (33)	29,864 (30)
3 or more births	68,863 (44)	47,268 (48)
<b>Smoking status</b>		
Never smoker	85,855 (55)	49,794 (51)
Former smoker	51,003 (32)	36,392 (37)
Current smoker	20,666 (13)	12,221 (12)
<b>Ever oral contraceptive use</b>	101,189 (64)	56,311 (57)
<b>Had tubal ligation</b>	34,717 (22)	20,595 (21)
<b>Had hysterectomy</b>	28,072 (18)	21,493 (22)
<b>Patent</b>	100,245 (63)	60,201 (61)
<b>Postmenopausal</b>	112,354 (71)	73,923 (75)
<b>Ever hormone therapy use</b>	57,768 (37)	38,616 (39)

Missing: Race (112 unexposed, 113 exposed), Education (298 unexposed, 294 exposed), BMI (587 unexposed, 339 exposed), Parity (1,050 unexposed, 827 exposed), Smoking status (560 unexposed, 533 exposed), Oral contraceptive use (34 unexposed, 10 exposed), Tubal ligation (193 unexposed, 233 exposed), Hysterectomy (56 unexposed, 40 exposed), Patent (168 unexposed, 177 exposed), Hormone therapy use (178 unexposed, 75 exposed)

**eTable 3.** Stratified Pooled Hazard Ratios (HRs) and 95% (CIs) for the Association Between Long-Term or Frequent Use of Powder in the Genital Area and Risk of Ovarian Cancer

	Long-term use <sup>a</sup> HR (95% CI)	Heterogeneity p-value	Frequent use <sup>a</sup> HR (95% CI)	Heterogeneity p-value
<b>Age at baseline</b>				
<60	1.13 (0.80, 1.60)	0.74	1.08 (0.95, 1.23)	0.62
≥60	0.96 (0.74, 1.25)		1.18 (0.82, 1.71)	
<b>Race</b>				
Non-Hispanic White	0.99 (0.80, 1.23)	0.52	1.08 (0.96, 1.22)	0.51
Other	1.26 (0.65, 2.45)		1.32 (0.63, 2.76)	
<b>Menopausal status<sup>b</sup></b>				
Premenopausal	NE <sup>c</sup>	NE <sup>c</sup>	1.07 (0.72, 1.57)	0.98
Postmenopausal	1.04 (0.84, 1.28)		1.10 (0.96, 1.24)	
<b>Follow-up time</b>				
0-10 years	1.08 (0.84, 1.39)	0.57	1.15 (0.93, 1.41)	0.69
>10 years	0.89 (0.61, 1.29)		1.06 (0.92, 1.24)	
<b>Hormone therapy use<sup>d</sup></b>				
Never	1.03 (0.74, 1.43)	0.68	1.01 (0.80, 1.27)	0.39
Ever	1.07 (0.81, 1.41)		1.24 (0.97, 1.59)	
<b>BMI</b>				
<30 kg/m <sup>2</sup>	1.00 (0.78, 1.28)	0.86	1.12 (0.99, 1.28)	0.39
>30 kg/m <sup>2</sup>	1.02 (0.70, 1.47)		0.90 (0.67, 1.20)	
<b>Parity</b>				
Nulliparous	0.59 (0.32, 1.12)	0.21	1.04 (0.70, 1.55)	0.51
Parous	1.10 (0.88, 1.37)		1.10 (0.97, 1.25)	
<b>Hysterectomy</b>				
No	1.00 (0.78, 1.28)	0.94	1.12 (0.98, 1.28)	0.75
Yes	1.06 (0.73, 1.53)		1.00 (0.75, 1.31)	
<b>Tubal ligation status</b>				
No	0.98 (0.78, 1.24)	0.83	1.15 (1.01, 1.31)	0.06
Yes	1.16 (0.71, 1.88)		0.74 (0.52, 1.05)	
<b>Patency</b>				
Patent	1.00 (0.76, 1.32)	0.99	1.19 (1.03, 1.37)	0.15
Not patent	1.03 (0.75, 1.41)		0.91 (0.73, 1.14)	

Adjusted for study, race/ethnicity (white, African-American, other), education <high school, some college, ≥college graduate), BMI (as a restricted cubic spline), parity (0, 1, 2, 3+ births), ever oral contraceptive use, tubal ligation (yes/no), hysterectomy status (yes/no), menopausal status (pre or postmenopausal), ever hormone therapy use. Variables being stratified on were not included in the adjustment set.

<sup>a</sup>Referent group = never users

<sup>b</sup>Menopausal status updated throughout follow-up.

<sup>c</sup>Not estimated due to low cell count for long-term exposed cases

<sup>d</sup>Among postmenopausal women only

**eTable 4.** Pooled Hazard Ratios and 95% CIs in Patent Women for Medically Confirmed Cases Overall and by Tumor Invasiveness, Location, and Histotype

	<b>Number of cases<sup>a</sup></b>	<b>Ever Use<sup>b</sup> (95% CI)</b>	<b>Long-term Use<sup>b</sup> (95% CI)</b>	<b>Frequent Use<sup>b</sup> (95% CI)</b>
<b>All medically-confirmed cases</b>	1,182	1.10 (0.98, 1.24)	1.04 (0.78, 1.38)	1.17 (1.00, 1.38)
<b>Invasiveness</b>				
Invasive only	973	1.13 (0.99, 1.28)	1.14 (0.84, 1.55)	1.21 (1.02, 1.44)
Borderline	87	1.03 (0.68, 1.58)	1.19 (0.39, 3.65)	1.09 (0.61, 1.94)
<i>Heterogeneity p-value<sup>c</sup></i>		0.70	0.88	0.42
<b>Tumor location</b>				
Epithelial Ovarian	973	1.14 (1.00, 1.29)	1.10 (0.81, 1.49)	1.21 (1.02, 1.45)
Fallopian Tube	30	1.46 (0.71, 2.96)	3.61 (0.69, 18.8)	2.20 (0.94, 5.15)
Peritoneal	62	0.93 (0.56, 1.54)	1.38 (0.29, 6.47)	0.79 (0.41, 1.52)
<i>Heterogeneity p-value<sup>c</sup></i>		0.59	0.32	0.01
<b>Histotype</b>				
Serous	635	1.14 (0.97, 1.33)	1.08 (0.73, 1.60)	1.18 (0.95, 1.46)
Endometrioid	107	1.30 (0.88, 1.91)	1.32 (0.49, 3.53)	1.42 (0.86, 2.34)
Mucinous	67	1.02 (0.63, 1.66)	1.41 (0.49, 4.03)	1.37 (0.72, 2.60)
Clear Cell	53	1.35 (0.80, 2.31)	1.29 (0.36, 4.58)	1.17 (0.53, 2.57)
Other	229	1.03 (0.79, 1.35)	1.23 (0.66, 2.28)	1.08 (0.74, 1.56)
<i>Heterogeneity p-value<sup>c</sup></i>		0.82	0.96	0.93
<b>Histotype II<sup>d</sup></b>				
High grade serous	435	1.16 (0.96, 1.40)	1.06 (0.68, 1.66)	1.20 (0.91, 1.58)
Low grade serous	17	1.20 (0.48, 3.01)	1.00 (0.94, 1.06)	0.50 (0.11, 2.30)
Other	400	1.09 (0.89, 1.33)	1.21 (0.76, 1.91)	1.21 (0.92, 1.59)
<i>Heterogeneity p-value<sup>c</sup></i>		0.91	0.25	0.48

Other ovarian cancers not meeting the specified case definition were censored at time of diagnosis

Adjusted for study, race/ethnicity (white, black, other), education  $\leq$ high school, some college,  $\geq$ college graduate), BMI (as a restricted cubic spline), parity (0, 1, 2, 3+ births), duration of oral contraceptive use (never, 0-5 years,  $>5$  years), menopausal status (pre or post-menopausal), duration of hormone therapy use (never, 0-5 years,  $>5$  years).

<sup>a</sup>For ever use analysis; limited to women with complete covariate information

<sup>b</sup>Referent group = Never users

<sup>c</sup>From competing risks model: likelihood ratio test of model that allows effect estimate to vary by subtype compared to a model that does not

<sup>d</sup>High grade serous defined as grade 2-4 serous or grade 3-4 endometrioid; Low grade serous = grade 1 serous

**eAppendix.** Questions Related to Use of Powder/Talc in the Genital Area in Each of the 4 Cohorts

**Nurses' Health Study: 1982 questionnaire** (underline in original questionnaire)

Have you ever commonly used talcum, baby powder or deodorizing powder to:

a. Apply to perineal (private) area?

Options: No; Daily; 1-6 times a week; less than once a week

b. Apply to sanitary napkins?

Options: No; Yes

**Ever use** defined as using ever on perineal area (a) or on sanitary napkins (b).

**Frequent use** defined as use on perineal area at least once per week. Participants who did not apply perineal talc but did apply talc to their sanitary napkins were considered to be non-frequent users for talc.

**Long term use** not assessed

**Nurses' Health Study II: 2013 questionnaire** (underline and CAPS in original questionnaire)

Have you ever used talcum, baby or deodorizing powder AT LEAST WEEKLY in the genital/rectal area or on sanitary napkins, tampons, or underwear?

Options: Never; Less than 1 year; 1 to <10 years; 10-<20 years; 20-<30 years; 30+ years

**Ever use** and **frequent use** defined as using at least weekly for any time period

**Long-term use** defined as using at least weekly for  $\geq 20$  years

**Sister Study: Baseline Questionnaire** (bold in original questionnaire)

During the ages of 10-13, about how often did you apply talcum powder to a **sanitary napkin, underwear, diaphragm, cervical cap, or directly to your vaginal area?** (Mark one.)

Options: Did not use; Sometimes; Frequently; Don't Know

In the past 12 months, how frequently have you applied talcum powder to a **sanitary napkin, underwear, diaphragm, cervical cap, or directly to your vaginal area?** (Mark one.)

Options: Did not use; Less than once a month; 1-3 times per month; 1-5 times per week; More than 5 times per month

In the past 12 months, what types of talcum powder have you usually used on a sanitary napkin, underwear, diaphragm, cervical cap, or your vaginal area? (Mark all that apply.)

Options: Did not use; Powder, Spray

Note: same questions were asked for talcum powder under arms and other parts of your body.

**Ever use** defined as use in 12 months prior to baseline or at ages 10-13.

**Frequent use** defined as use at least once per week (in the last 12 months) or "frequently" during ages 10-13.

**Long-term use** defined as perineal use at ages 10-13 and in the last 12 months.

Women who said they were non-users at one time point but who were missing data for the other were considered never users.

**Women's Health Initiative: Observational Study Baseline Questionnaire**

Have you ever used powder on your private parts (genital areas)?

Options: No; Yes

For how many years?

Options: Less than 1 year; 1-4 years; 5-9 years; 10-19 years; 20 or more years

*Did you ever use a diaphragm (a birth control device that fits over the opening of your womb)?*

*Options: No, Yes*

Did you ever use powder on your diaphragm?

Options: No; Yes

For how many years did you use powder on your diaphragm?

Options: Less than 1 year; 1-4 years; 5-9 years; 10-19 years; 20 or more years

Did you ever use powder on a sanitary napkin or pad?

Options: No; Yes

For how many years did you use powder on sanitary pads?

Options: Less than 1 year; 1-4 years; 5-9 years; 10-19 years; 20 or more years

**Ever use** defined as “Yes” to any of 3 ‘ever use’ questions

**Frequent use** not assessed

**Long term use** defined as use for 20 or more years on any of 3 ‘years used’ questions